

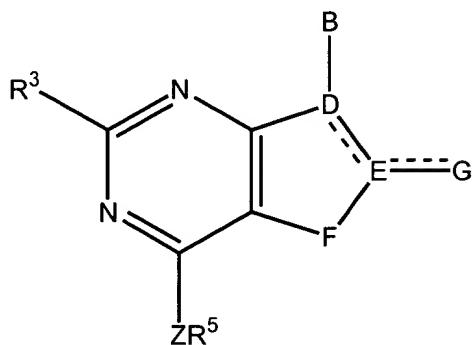
application. A final rejection issued on June 27, 2001. The present response is submitted within one year of the period set for response to thereto.

Please amend the application as follows:

IN THE CLAIMS

Amend claims 18 and 25 to read as follows:

18. A compound of the formula



wherein the dashed lines represent optional double bonds;

B is $-\text{NR}^1\text{R}^2$, $-\text{CR}^1\text{R}^2\text{R}^{10}$, $-\text{C}(\text{=CR}^2\text{R}^{11})\text{R}^1$, $-\text{NHCR}^1\text{R}^2\text{R}^{10}$, $-\text{OCR}^1\text{R}^2\text{R}^{10}$, $-\text{SCR}^1\text{R}^2\text{R}^{10}$, $\text{CR}^2\text{R}^{10}\text{NHR}^1$, $-\text{CR}^2\text{R}^{10}\text{OR}^1$, $-\text{CR}^2\text{R}^{10}\text{SR}^1$ or $-\text{COR}^2$;

E is nitrogen, CH or carbon;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is double bonded to E, or D is CH and is single bonded to E;

F is CHR^4 or NR^4 ; provided that either 1) exactly one of D or E is nitrogen and F is CHR^4 or 2) F is NR^4 and neither D nor E is nitrogen;

G, when single bonded to E is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $-\text{S}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{O}(\text{C}_1\text{-C}_4\text{ alkyl})$, NH_2 , $-\text{NH}(\text{C}_1\text{-C}_4\text{ alkyl})$ or $-\text{N}(\text{C}_1\text{-C}_2\text{ alkyl})(\text{C}_1\text{-C}_4\text{ alkyl})$ wherein each of the $\text{C}_1\text{-C}_4$ alkyl groups of G may optionally be substituted by one hydroxy, $-\text{O}(\text{C}_1\text{-C}_2\text{ alkyl})$ or fluoro group; and G when double bonded to E is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D, is absent;

R^1 is hydrogen, C_1 - C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1 - C_4 alkoxy, CF_3 , $-C(=O)O-(C_1-C_4)alkyl$, $-OC(=O)(C_1-C_4)alkyl$, $OC(=O)N(C_1-C_4)alkyl(C_1-C_2)alkyl$, $-NHCO(C_1-C_4)alkyl$, $-COOH$, $-COO(C_1-C_4)alkyl$, $-CONH(C_1-C_4)alkyl$, $-CON(C_1-C_4)alkyl(C_1-C_2)alkyl$, $-S(C_1-C_4)alkyl$, $-CN$, NO_2 , $-SO(C_1-C_4)alkyl$, $-SO_2(C_1-C_4)alkyl$, $-SO_2NH(C_1-C_4)alkyl$, $SO_2N(C_1-C_4)alkyl(C_1-C_2)alkyl$, wherein a carbon-carbon single bond of each of the C_1 - C_4 alkyl groups in the foregoing R^1 groups having at least two carbons may optionally be replaced with a carbon-carbon double or triple bond, and one or two carbon-carbon single bonds of each of the C_1 - C_4 alkyl groups in the foregoing R^1 groups having four carbon atoms may optionally be replaced with a carbon-carbon double or triple bond; R^2 is C_1 - C_{12} alkyl wherein one carbon-carbon single bond of any said alkyl group having at least two carbons, one or two carbon-carbon single bonds of any alkyl having at least four carbons, and from one to three carbon-carbon single bonds of any said alkyl having at least six carbons may optionally be replaced with a carbon-carbon double or triple bond; or R^2 is aryl or $(C_1-C_4)alkylene$ aryl, wherein said aryl and the aryl moiety of said $(C_1-C_4)alkylene$ aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; or R^2 is C_3 - C_8 cycloalkyl or $(C_1-C_6)alkylene(C_3-C_8)cycloalkyl$, wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said $(C_1-C_6)alkylene(C_3-C_8)cycloalkyl$ may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1 - C_4 alkyl, benzyl and C_1 - C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1 - C_4 alkyl, or with one substituent selected from bromo, iodo, C_1 - C_6 alkoxy, $-OC(=O)(C_1-C_4)alkyl$, $OC(=O)N(C_1-C_4)alkyl(C_1-C_2)alkyl$, $-S(C_1-C_6)alkyl$, amino, $-NH(C_1-C_2)alkyl$, $-N(C_1-C_2)alkyl(C_1-C_4)alkyl$, $-N(C_1-C_4)alkyl-CO-(C_1-C_4)alkyl$, $-NHCO(C_1-C_4)alkyl$, $-COOH$, $-COO(C_1-C_4)alkyl$, $-CONH(C_1-C_4)alkyl$, $CON(C_1-C_4)alkyl(C_1-C_2)alkyl$, $-SH$, $-CN$, $-NO_2$, $-SO(C_1-C_4)alkyl$, $-SO_2(C_1-C_4)alkyl$, $-SO_2NH(C_1-C_4)alkyl$ and $-SO_2N(C_1-C_4)alkyl(C_1-C_2)alkyl$;

$-NR^1R^2$ or $-CR^1R^2R^{10}$ may form a 3 to 8 membered ring, that in the case of $-CR^1R^2R^{10}$ is carbocyclic, said ring consisting of single bonds, wherein, when said ring has from 5 to 8 members, one or two of the ring carbon atoms of such a 5 to 8 membered ring may optionally and

independently or replaced by an oxygen or sulfur atom or by NZ³ wherein Z³ is hydrogen, C₁-C₄ alkyl, benzyl and C₁-C₄ alkanoyl, and wherein from one to three of the single bonds of such a 3 to 8 membered ring that are carbon-carbon or carbon-nitrogen single bonds may each optionally be replaced by a double bond;

R³ is hydrogen, C₁-C₄ alkyl, O(C₁-C₄ alkyl), chloro, fluoro, bromo, iodo, -CN, -S(C₁-C₄ alkyl) or -SO₂(C₁-C₄ alkyl) wherein each of the (C₁-C₄ alkyl) moieties in the foregoing R³ groups may optionally be substituted with one substituent R⁹ selected from hydroxy, fluoro and (C₁-C₂ alkoxy);

each of R⁴ is, independently hydrogen, (C₁-C₆ alkyl), fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, cyano, amino, nitro, -O(C₁-C₄ alkyl), N (C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₄ alkyl), -SO(C₁-C₄ alkyl), -SO₂(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), -C(=O)H or C(=O)O(C₁-C₄ alkyl), wherein one or two of the carbon-carbon single bonds in each of the (C₁-C₆ alkyl) and (C₁-C₄ alkyl) moieties in the foregoing R⁴ groups may optionally be replaced with a carbon-carbon double or triple bond and wherein each of said (C₁-C₆ alkyl) and (C₁-C₄ alkyl) moieties may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C₁-C₃ alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH₃, fluoro, chloro, -CN, -COOH, -C(=O)O(C₁-C₄ alkyl), -C(=O)(C₁-C₄ alkyl) and NO₂;

R⁵ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C₃-C₈ cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ⁴ wherein N⁴ is hydrogen, C₁-C₄ is alkyl or benzyl; and wherein each of the foregoing R⁵ groups is substituted with from one to four substituents wherein one to three of said substituents may be selected, independently, from chloro, C₁-C₆ alkyl and -O(C₁-C₆ alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, -CF₃, -NO₂, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₆ alkyl), -C(=O)O(C₁-C₄ alkyl), -C(=O)(C₁-C₄ alkyl), -COOH, -SO₂NH(C₁-C₄ alkyl), -SO₂N (C₁-C₂ alkyl) (C₁-C₄ alkyl), -SO₂NH₂, NHSO₂(C₁-C₄ alkyl), -S(C₁-C₆

alkyl) and $\text{-SO}_2(\text{C}_1\text{-C}_6\text{ alkyl})$, and wherein each of the $\text{C}_1\text{-C}_4$ alkyl and $\text{C}_1\text{-C}_6$ alkyl, moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl; and furthermore wherein when R^5 is phenyl or pyridyl substituted with three substituents; said substituents can further be selected from $(\text{C}_1\text{-C}_4\text{ alkyl})\text{O}(\text{C}_1\text{-C}_4\text{ alkyl})$, OCF_3 , and fluoro, and one carbon-carbon single bond of each $(\text{C}_1\text{-C}_4)$ alkyl group of said substituents having between two and four carbon atoms may be optionally replaced with a carbon-carbon double or triple bond; or R^5 is pyrimidyl substituted by three substituents independently selected from $\text{C}_1\text{-C}_4$ alkyl, $\text{-O}(\text{C}_1\text{-C}_4\text{ alkyl})$, CF_3 , OCF_3 , -CHO , $(\text{C}_1\text{-C}_4\text{ alkyl})\text{-OH}$, CN , Cl , F , Br , I and NO_2 , wherein a carbon-carbon single bond of said $(\text{C}_1\text{-C}_4)$ alkyl groups having been two and four carbon atoms may optionally be replaced by a carbon-carbon double or triple bond;

R^7 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, halo, cyano, hydroxy, $\text{-O}(\text{C}_1\text{-C}_4\text{ alkyl})\text{-C}(=\text{O})(\text{C}_1\text{-C}_4\text{ alkyl})$, $\text{-C}(=\text{O})\text{O}(\text{C}_1\text{-C}_4\text{ alkyl})$, -OCF_3 , -CF_3 , $\text{-CH}_2\text{-OH}$, $\text{-CH}_2\text{O}(\text{C}_1\text{-C}_4\text{ alkyl})$;

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

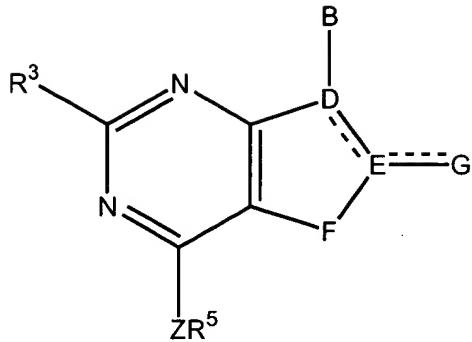
R^{11} is hydrogen or $\text{C}_1\text{-C}_4$ alkyl; and

with the proviso that: (a) when R^4 is attached to nitrogen, it not halo, cyano or nitro; and (b) one of E, D and F must be nitrogen or substituted nitrogen, and only one of E, D and F can be nitrogen or substituted nitrogen;

Z is NH, oxygen, sulfur, $\text{-N}(\text{C}_1\text{-C}_4\text{ alkyl})$, $\text{-NC}(=\text{O})(\text{C}_1\text{-C}_2\text{ alkyl})$ $\text{NC}(\text{-O})\text{O}(\text{C}_1\text{-C}_2\text{ alkyl})$ or $\text{CR}^{13}\text{R}^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14} can be cyano;

or a pharmaceutically acceptable salt of such compound.

25. A compound of the formula



wherein the dashed lines represent optional double bonds;

B is $-\text{NR}^1\text{R}^2$, $-\text{CR}^1\text{R}^2\text{R}^{10}$, $-\text{C}(\text{=CR}^2\text{R}^{11})\text{R}^1$, $-\text{NHCR}^1\text{R}^2\text{R}^{10}$, $-\text{OCR}^1\text{R}^2\text{R}^{10}$, $-\text{SCR}^1\text{R}^2\text{R}^{10}$, $\text{CR}^2\text{R}^{10}\text{NHR}^1$, $-\text{CR}^2\text{R}^{10}\text{OR}^1$, $-\text{CR}^2\text{R}^{10}\text{SR}^1$ or $-\text{COR}^2$;

E is nitrogen, CH or carbon;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is double bonded to E, or D is CH and is single bonded to E;

F is CHR^4 or NR^4 ; provided that either 1) exactly one of D or E is nitrogen and F is CHR^4 or 2) F is NR^4 and neither D nor E is nitrogen;

G, when single bonded to E is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, $-\text{S}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{O}(\text{C}_1\text{-C}_4\text{ alkyl})$, NH_2 , $-\text{NH}(\text{C}_1\text{-C}_4\text{ alkyl})$ or $-\text{N}(\text{C}_1\text{-C}_2\text{ alkyl})(\text{C}_1\text{-C}_4\text{ alkyl})$ wherein each of the $\text{C}_1\text{-C}_4$ alkyl groups of G may optionally be substituted by one hydroxy, $-\text{O}(\text{C}_1\text{-C}_2\text{ alkyl})$ or fluoro group; and G when double bonded to E is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D, is absent;

R^1 is hydrogen, $\text{C}_1\text{-C}_6$ alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, $\text{C}_1\text{-C}_4$ alkoxy, CF_3 , $-\text{C}(\text{=O})\text{O}-(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{OC}(\text{=O})(\text{C}_1\text{-C}_4\text{ alkyl})$, $\text{OC}(\text{=O})\text{N}(\text{C}_1\text{-C}_4\text{ alkyl})(\text{C}_1\text{-C}_2\text{ alkyl})$, $-\text{NHCO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{COOH}$, $-\text{COO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{CONH}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{CON}(\text{C}_1\text{-C}_4\text{ alkyl})(\text{C}_1\text{-C}_2\text{ alkyl})$, $-\text{S}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{CN}$, NO_2 , $-\text{SO}(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{SO}_2(\text{C}_1\text{-C}_4\text{ alkyl})$, $-\text{SO}_2\text{NH}(\text{C}_1\text{-C}_4\text{ alkyl})$, $\text{SO}_2\text{N}(\text{C}_1\text{-C}_4\text{ alkyl})(\text{C}_1\text{-C}_2\text{ alkyl})$, wherein a carbon-carbon single bond of each of the $\text{C}_1\text{-C}_4$ alkyl groups in the foregoing R^1 groups having at least two carbons may optionally be replaced with a carbon-carbon double or triple bond, and one or two carbon-carbon single bonds of each of the $\text{C}_1\text{-C}_4$ alkyl groups in the

foregoing R¹ groups having four carbon atoms may optionally be replaced with a carbon-carbon double or triple bond; R² is C₁-C₁₂ alkyl wherein one carbon-carbon single bond of any said alkyl group having at least two carbons, one or two carbon-carbon single bonds of any alkyl having at least four carbons, and from one to three carbon-carbon single bonds of any said alkyl having at least six carbons may optionally be replaced with a carbon-carbon double or triple bond; or R² is aryl or (C₁-C₄ alkylene)aryl, wherein said aryl and the aryl moiety of said (C₁-C₄ alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; or R² is C₃-C₈ cycloalkyl or (C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C₁-C₆ alkylene)(C₃-C₈ cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ² wherein Z² is selected from hydrogen, C₁-C₄ alkyl, benzyl and C₁-C₄ alkanoyl, and wherein each of the foregoing R² groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C₁-C₄ alkyl, or with one substituent selected from bromo, iodo, C₁-C₆ alkoxy, -OC(=O)(C₁-C₆ alkyl), OC(=O)N (C₁-C₄ alkyl)(C₁-C₂ alkyl), -S(C₁-C₆ alkyl), amino, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)-CO-(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COOH, -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SH, -CN, -NO₂, -SO(C₁-C₄ alkyl), -SO₂(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl) and -SO₂N (C₁-C₄ alkyl)(C₁-C₂ alkyl);

-NR¹R² or -CR¹R²R¹⁰ may form a 3 to 8 membered ring, that in the case of -CR¹R²R¹⁰ is carbocyclic, said ring consisting of single bonds, wherein, when said ring has from 5 to 8 members, one or two of the ring carbon atoms of such a 5 to 8 membered ring may optionally and independently be replaced by an oxygen or sulfur atom or by NZ³ wherein Z³ is hydrogen, C₁-C₄ alkyl, benzyl and C₁-C₄ alkanoyl, and wherein from one to three of the single bonds of such a 3 to 8 membered ring that are carbon-carbon or carbon-nitrogen single bonds may each optionally be replaced by a double bond;

R³ is hydrogen, C₁-C₄ alkyl, O(C₁-C₄ alkyl), chloro, fluoro, bromo, iodo, -CN, -S(C₁-C₄ alkyl) or -SO₂(C₁-C₄ alkyl) wherein each of the (C₁-C₄ alkyl) moieties in the foregoing R³ groups may optionally be substituted with one substituent R⁹ selected from hydroxy, fluoro and (C₁-C₂

alkoxy);

each of R^4 is, independently hydrogen, (C_1 - C_6 alkyl), fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, cyano, amino, nitro, $-O(C_1$ - C_4 alkyl), $N(C_1$ - C_4 alkyl)(C_1 - C_2 alkyl), $-S(C_1$ - C_4 alkyl), $-SO(C_1$ - C_4 alkyl), $-SO_2(C_1$ - C_4 alkyl), $-CO(C_1$ - C_4 alkyl), $-C(=O)H$ or $C(=O)O(C_1$ - C_4 alkyl), wherein one or two of the carbon-carbon single bonds in each of the (C_1 - C_6 alkyl) and (C_1 - C_4 alkyl) moieties in the foregoing R^4 groups may optionally be replaced with a carbon-carbon double or triple bond and wherein each of said (C_1 - C_6 alkyl) and (C_1 - C_4 alkyl) moieties may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C_1 - C_3 alkoxy, dimethylamino, methylamino, ethylamino, $-NHC(=O)CH_3$, fluoro, chloro, $-CN$, $-COOH$, $-C(=O)O(C_1$ - C_4 alkyl), $-C(=O)(C_1$ - C_4 alkyl) and NO_2 ;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3 - C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein N^4 is hydrogen, C_1 - C_4 is alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents wherein one to three of said substituents may be selected, independently, from chloro, C_1 - C_6 alkyl and $-O(C_1$ - C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, $-CN$, $-CF_3$, $-NO_2$, $-NH_2$, $-NH(C_1$ - C_4 alkyl), $-N(C_1$ - C_2 alkyl)(C_1 - C_6 alkyl), $-C(=O)O(C_1$ - C_4 alkyl), $-C(=O)(C_1$ - C_4 alkyl), $-COOH$, $-SO_2NH(C_1$ - C_4 alkyl), $-SO_2N(C_1$ - C_2 alkyl)(C_1 - C_4 alkyl), $-SO_2NH_2$, $NHSO_2(C_1$ - C_4 alkyl), $-S(C_1$ - C_6 alkyl) and $-SO_2(C_1$ - C_6 alkyl), and wherein each of the C_1 - C_4 alkyl and C_1 - C_6 alkyl, moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, C_1 - C_4 alkyl, halo, cyano, hydroxy, $-O(C_1$ - C_4 alkyl) $-C(=O)(C_1$ - C_4 alkyl), $-C(=O)O(C_1$ - C_4 alkyl), $-OCF_3$, $-CF_3$, $-CH_2OH$, $-CH_2O(C_1$ - C_4 alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1 - C_4 alkyl; and

with the proviso that: (a) when R^4 is attached to nitrogen, it not halo, cyano or nitro; and (b)